REMARKS

Claims 10, 12-20, 27-29, 31, 34-37, 39-44, 47-51, 54-57 and 61-67 are pending after the present amendments. New claims 61-67 have been added. Claim 10 has been amended to relate to agglomerates prepared using a nozzle sprayer. The amendments are supported at least in the specification at page 6, lines 15-21 and at page 9, lines 24-27. Thus, no new matter is added. Applicants respectfully request reconsideration in view of the remarks below.

Rejections under 35 U.S.C. § 112, first and second paragraphs

The Office rejected claims 10, 12-14, 16-20, 27-28, 31, 34-37, 39-44, 47-51 and 54-60 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The claims have been amended for clarity. As amended, the claims no longer recite the terms objected to. Thus, Applicants respectfully request that these rejections be withdrawn.

The Office also rejected claims 10, 12-14, 16-20, 27-28, 31, 34-37, 39-44, 47,-51 and 54-60 under 35 U.S.C. § 112, first and second paragraphs. More particularly, the Office alleges that the "full scope is clearly not enabled, since [a prior art] procedure will not give the right product." (Office action, page 4). The Office also alleges that "the claims do not particularly point out and distinctly claim the actual process that does produce the non-needle, non-rosette form actually produced." (Office Action, page 4). Applicants disagree, and address the rejections in view of the amended claims.

As amended, the process specifically recites the use of a nozzle sprayer to contact the solution or suspension with the anti-solvent under stirring to produce the desired agglomerates. Unlike the process as claimed, the prior art fails to teach the use of a nozzle sprayer and a stirring device in contacting a potassium clavulanate solution or suspension with an anti-solvent, to control the properties of the agglomerate produced. Thus, Applicants respectfully submit that the claims are enabled and comply with the written description, and request that this rejection be withdrawn.

Furthermore, the Office also indicated that the claims fail to require that one of the solvents be water, and thus are broader than what the specification sets forth. (Office action, page

5). To expedite prosecution, the claims have been amended to recite a process having water present in the solvent. Applicants therefore respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 102

The Office rejected claims 37, 40-42, 44, 46-51 and 58-60 under 35 U.S.C. § 102(b), as allegedly being anticipated by U.S. patent nos. 4,454,069, 6,417,352, 5,288,861, 5,985,625, U.S. patent application publication 2003/0022882 ('882), or WO 98/21212. The Office also alleged that "Applicants argue that needles would be expected, but give no reasoning." (Office action, page 6). Applicants respectfully disagree, and address the rejections in view of the amended claims.

U.S. patent 5,288,861 describes potassium clavulanates in rosette form, where a plurality of needle crystals radiate out from a common nucleation point. Rosette crystals are obtained from an "inverse precipitation" procedure, where the clavulanate solution is added to the precipitating diluent. (See '861 patent at col. 4:18-24). For example, a solution of potassium clavulanate is added to an isopropanol/acetone precipitating diluent. (See, Examples 1-3). Alternatively, a solution of t-butylamine clavulanate may be added to a mixture of potassium ethyl hexanoate. (See, Examples 4-8). As rosette-like crystalline forms of potassium clavulanates have been excluded in the proviso, this patent does not anticipate the agglomerates as claimed.

U. S. patents 4,454,069, 5,985,625, 6,417,352, the '882 application and WO 98/21212 describe clavulanates prepared using a "normal" precipitation procedure in which the precipitating diluent is added to the solution of the material to be crystallized. More particularly, a solution of a potassium source (e.g. potassium ethylhexanoate) is added to a solution, suspension or slurry of an amine salt of clavulanic acid, or to a solution of clavulanic acid. The processes are described in more detail as follows:

In Example 4 of U.S. patent 4,454,069, potassium ethyl hexanoate in isopropanol is added to a solution of tert-butylamine salt of clavulanic acid. The resulting mixture was stirred at ambient temperature for 30 minutes, and chilled at 0^{o} - 5^{o} C.

In Example 3 of U.S. patent 5,985,625, potassium 2-ethyl-hexanoate is added to N,N'-diisopropylethyleneammonium diclavulanate. The obtained suspension was cooled to 0° - 5° C.

In Examples 8-10 of U.S. patent 6,417,352, a solution of potassium 2-ethylhexanoate is added to a solution of clavulanic acid. The mixture was cooled to 5° C.

In Example 4 of U.S. patent application publication 2003/0022882, potassium-2-ethylhexanoate in isopropanol is added to a solution of 2-amino-2,4-4-trimethylpentane salt of clavulanic acid in isopropanol. The mixture was cooled to 0° - 5° C.

In Examples 6 and 8 of WO 98/21212, a solution of potassium 2-ethylhexanoate in acetone is added to a suspension of bis(2-(dimethylamino)ethyl)ether diclavulanate in acetone and water. The mixture in Example 6 was cooled to 5° C, whereas the mixture in Example 8 was cooled to 10° C. Example 8 also explicitly defines the formation of potassium clavulanate clusters as needles.

Although the prior art cited above may not specify the form of the crystals, it is generally known in the art that normal precipitation processes described above form needles. The '069 patent having the earliest filing date, describes clavulanate crystals obtained via ion replacement for the first time, and explicitly describes the form of the resulting crystals obtained. Depending on process conditions, such as the amine salt, the solvent, or the use of a solution or suspension, the needles may differ in size. The needles are generally large, long crystals, sometimes agglomerated into plate-like crystals, and sometimes randomly aggregated into loosely formed bundles.

Regardless of whether the needles form loosely formed bundles, individual needles will always be present and visible upon microscopic examination. (See, Exhibit 1, bottom portion). In contrast, the top portion shows an electron-microscope photograph of potassium agglomerates prepared using a nozzle sprayer and a stirring device. As this picture shows, the agglomerates of the claimed invention contain substantially no potassium clavulanate in the needle form. Although the mechanism of agglomerate formation is not necessary to practice the invention as claimed, the different physical characteristics of the agglomerates may be attributable to the method of

contacting the potassium clavulanate containing solution and the anti-solvent, such as the use of spray nozzles or capillaries. For instance, the amount of nozzles, the nozzle diameter, and the flow through the nozzles may be used to control the average particle size and density of the agglomerates. (See specification at page 9, lines 18-27).

Furthermore, potassium clavulanate needles have different physical characteristics than agglomerates of the claimed invention, as indicated in Example 8 of the specification. For instance, potassium clavulanate needles have a low bulk density which gives rise to processing difficulties. (See, U.S. patent 5,288,861 at col. 1: 41-49; see also, specification at page 1, line 31 through page 2, line 2). As shown in Example 8, potassium clavulanate needles have a loose bulk density and a tapped bulk density that are significantly lower than agglomerates that are substantially free from needles. Potassium clavulanate needles also have a higher compressibility of about 50 %, compared to agglomerates substantially free from needles, which have a lower compressibility between about 10 % and 40 %.

The process used in Example 8 to obtain needles is similar to those described in the prior art. In particular, a solution of potassium 2-ethylhexanoate at 5-10 °C is added to a suspension of an amine salt of clavulanic acid (*i.e.*, diclavulanate salt of bis(2-dimethylaminoethyl)ether). The cooling temperature at 5-10 °C is similar to Examples 6 and 8 of WO 98/21212, which described the formation of potassium clavulanate needle crystals.

Based on the above, none of the prior art cited above describes the agglomerates as claimed. Thus, claims 37, 40-42, 44, 46-51 and 58-60 are not anticipated by U.S. patent nos. 4,454,069, 6,417,352, 5,288,861, 5,985,625, U.S. patent application publication 2003/0022882 ('882), or WO 98/21212. Applicants therefore, respectfully request that these rejections be withdrawn.

The Office also rejected claims 37, 39-44 and 46-52 under 35 U.S.C. § 102(b), as allegedly being anticipated by WO 97/33564. More particularly, the Office alleged that "Examples 7-11 all have Potassium clavulanate in the agglomerate." (Office action, pages 7-8). Applicants disagree.

The auxiliary-free agglomerates disclosed in WO 97/33564 relate to β-lactam antibiotics other than clavulanic acid, which are prepared by extrusion. In particular, only agglomerates of penicillin V potassium, phenoxymethylpenicillin potassium, amoxicillin trihydrate, and cephalexin monohydrate are described. (WO 97/33564, Examples 1-6). Potassium clavulanate is mentioned only as a compound in powder form that can be mixed with the auxiliary-free agglomerates. (See WO 97/33564 at page 9, lines 17 and 21-22; and at page 11, lines 4-5 and 18-19). For instance, agglomerates of a β-lactam antibiotic may be mixed with dry potassium clavulanate and optional auxiliaries, and compressed into tablets (WO 97/33564 at page 11, lines 17-25). Examples 7-9 describe how agglomerates of amoxillin trihydrate is mixed with potassium clavulanate. The mixing does not change the characteristics of the ingoing constituents, and the potassium clavulanate remains a powder mixed with the agglomerated amoxycillin trihydrate.

As powders are not agglomerates, no potassium clavulanate agglomerate is disclosed. The prior art itself notes the difference between powders and agglomerates, specifying that "agglomerates should not disintegrate into a powder because this would negatively affect the free-flow capability." (WO 97/33564, page 8, lines 1-2). It is also generally known that antibiotic compounds in powder form are not suitable for formulation purposes. These powders generally "perform badly as far as flowability is concerned, which causes problems in the manufacturing of final dosage forms, such as tablets." (See specification, page 1, lines 26-29). Unlike powders, the agglomerates as claimed have a high bulk density, an improved flowability and less compressibility. Due to the excellent flowability of the agglomerates prepared using the present methods, the agglomerates can be used for direct compression of tablets without the need for further pre-granulation. (See, specification at page 12, lines 6-21).

Based on the above, WO 97/33564 fails to teach the agglomerates of the present invention. Thus, claims 37, 39-44 and 46-52 are not anticipated. Applicants therefore respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

The Office rejected claims 10, 12-14, 16-20, 27-28, 31, 34-37, 42-44, 47-51 and 54-60 under 35 U.S.C. § 103(a), as allegedly being unpatentable under Box. Applicants respectfully disagree.

US 4,072,569 neither teaches nor suggests a process for preparing an agglomerate by precipitation. Example 4 which the Office cited describes a process for preparing sodium clavulanate tetrahydrate by hydrogenation of benzyl clavulanate. Sodium clavulanate was crystallized by evaporation in vacuo from a water acetone mixture. Unlike the invention as claimed, a crystallization by evaporation is completely different from agglomeration by precipitation of dissolved material in an antisolvent.

Furthermore, there is no reasonable expectation of success that the process described in the '569 patent would yield the agglomerates of the invention as claimed. More particularly, clavulanate tetrahydrates have different solubility and precipitating properties than the usual clavulanate. Thus, claims 10, 12-14, 16-20, 27-28, 31, 34-37, 42-44, 47-51 and 54-60 are not obvious under U.S. patent 4,072,569, and Applicants request that this rejection be withdrawn.

New claims 61-67

New claims 61-67 are dependent on claim 10, and contain all the limitations of claim 10. Based on the above, claim 10 is novel and non-obvious. Accordingly, new claims 61-67 are also novel and non-obvious. Applicants therefore respectfully request that these claims be passed to allowance.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 246152015300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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